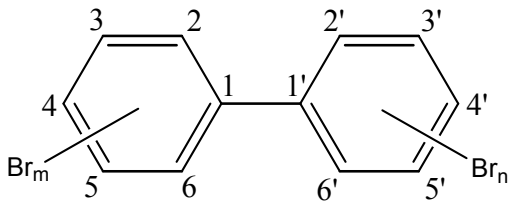
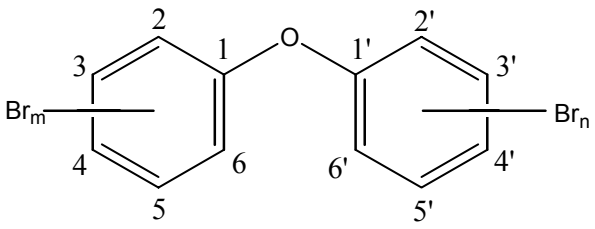
2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO POLYBROMINATED BIPHENYLS AND POLYBROMINATED DIPHENYL ETHERS IN THE UNITED STATES

Polybrominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs) are brominated organic compounds used as flame retardant additives in plastics, textiles, and other materials. As additives, they are physically mixed into product applications, rather than chemically bound. Therefore, they have the potential to migrate from the plastic matrix into the environment. Commercial production of PBBs began in approximately 1970 and manufacture was discontinued in the United States in 1976, subsequent to a major agricultural contamination episode that occurred in Michigan in 1973. Concern regarding the health effects of PBBs is mainly related to exposures that have resulted from the regionally localized Michigan episode. Production of PBDEs also began in the 1970s but, unlike PBBs, has continued to the present. Concern for the possible health effects of PBDEs has heightened recently due to evidence that these chemicals are ubiquitously distributed with levels in the environment, biota, and humans tissues and breast milk that are continually increasing.

PBBs and PBDEs are each classes of structurally similar brominated hydrocarbons in which 2–10 bromine atoms are attached to the molecular structure (i.e., biphenyl for PBBs; diphenyl ether for PBDEs). Monobrominated structures (i.e., one bromine atom attached to the molecule) are often included when describing PBBs and PBDEs. There are 209 different molecular combinations, or congeners, that are possible for both PBBs and PBDEs. Based on the number of bromine substituents, there are 10 homologous groups of PBB and PBDE congeners (monobrominated through decabrominated), with each homologous group containing one or more isomers. The mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and decabromo-congeners can exist in 3, 12, 24, 42, 46, 42, 24, 12, 3, and 1 isomers, respectively. The general chemical structures of PBBs and PBDEs are similar when viewed in one dimension, differing only in an ether linkage, as shown below, where m+n = 1–10:

 where m + n = 1 to 10	 where m + n = 1 to 10
PBBs	PBDEs

However, due to the ether linkage and position/number of bromine atoms, there are important three-dimensional differences in the structures of PBBs and PBDEs that can influence the molecules' receptor interactions and toxicological properties as discussed in Section 3.5, Mechanisms of Action.

People are environmentally exposed to PBBs and PBDEs of different congeneric composition than the source commercial mixtures, due to differential partitioning and transformation of the individual congeners in the environment, including transformation in food animals (e.g., dairy cattle in the case of PBBs). Additionally, as discussed in Section 3.4, because PBBs and PBDEs are lipophilic and some congeners are not readily metabolized, they are likely to be retained in the body for long periods of time (years).

Polybrominated Biphenyls. Three commercial PBB mixtures were manufactured: hexabromobiphenyl, octabromobiphenyl, and decabromobiphenyl. The two main commercial hexabromobiphenyl PBB mixtures had the trade names FireMaster BP-6 and FireMaster FF-1. FireMaster FF-1 was produced by grinding FireMaster BP-6 and adding 2% calcium polysilicate as an anticaking agent. The hexabrombiphenyl mixtures contained varying proportions of di- through octabrominated homologues. 2,2',4,4',5,5'-Hexabromobiphenyl is the most abundant congener in the mixtures (53.9–68.0%), followed by 7.0–27.3% of 2,2',3,4,4',5,5'-heptabromobiphenyl. Commercial octabromobiphenyl mixtures contained a large proportion (47.4–60.0%) of nonabromobiphenyl congeners, whereas commercial decabromobiphenyls contain predominately (96.8%) decabromobiphenyl congener.

Limited data are available on health effects of commercial decabromobiphenyl and octabromobiphenyl mixtures, although the hexabromobiphenyl mixtures FireMaster BP-6 and FireMaster FF-1 have been extensively tested. Most of the information on human health effects of PBBs comes from studies of Michigan residents who accidentally ingested milk, meat, and eggs that came from farms that used animal feed contaminated with FireMaster FF-1. In 1973, livestock on certain farms in Michigan were exposed

to FireMaster FF-1 after it was mistaken as a feed supplement and mixed with feed that was distributed within the state for several months before being discovered. Health problems in dairy cattle, reported in the fall of 1973, were the first signs that this episode occurred, but the accidental addition of PBBs to animal feed was not identified as the cause of the problem until the spring of 1974.

Available information on the metabolism of PBBs in livestock is insufficient to ascertain whether the people affected in Michigan ingested the original PBB mixtures or metabolic products of the PBBs. Based on limited information in dairy cattle and additional data in laboratory animals as discussed in Section 3.4.2.2, it is reasonable to assume that mainly unchanged penta-, hexa-, and heptabromobiphenyl congeners were consumed in animal products during the contamination episode. PBBs were excreted in cattle manure and, as such, were also environmentally distributed in Michigan via waste disposal on farms. The general population outside of Michigan could possibly have been exposed to PBBs by the oral route via the food chain, and the inhalation and dermal routes represent the most likely routes of exposure to PBBs in occupational settings.

Polybrominated Diphenyl Ethers. Three commercial PBDE mixtures have been and continue to be produced: decabromodiphenyl ether, octabromodiphenyl ether, and pentabromodiphenyl ether. DecaBDE has accounted for more than 80% of PBDE usage. The composition of commercial decaBDE is $97% pure with the remainder mainly nonaBDE. Commercial octaBDE is a mixture of congeners ranging from nona- to hexaBDE, and mixtures of pentaBDE are comprised of tetra-, penta-, and hexaBDE congeners. Congeners with less than four bromine atoms are generally not found in commercial PBDEs. DecaBDE seems to be largely resistant to environmental degradation, whereas differential partitioning and transformation of the octa- and hexaBDE mixture components have more readily yielded the predominance of lower-brominated tetra- and penta-congeners, particularly 2,2',4,4'-tetraBDE and 2,2',4,4',5-pentaBDE, which have been detected in environmental and human tissue samples (including breast milk). The main source of human exposure to PBDEs may be the diet, particularly foods with high fat content such as fatty fish. PBDEs have been detected in air samples, including those taken from remote areas, indicating that inhalation is also an exposure route for the general population.

2.2 SUMMARY OF HEALTH EFFECTS

Polybrominated Biphenyls. Much of the information on human health effects of PBBs comes from studies of Michigan populations where PBBs were accidentally introduced into the feed/food chain. There is also some information on health effects in chemical workers. Although these studies consist largely of observations on groups that are not well defined and lack accurate intake data, they do provide a picture of the health status of the affected people and an indication of potential effects for the general population who may be exposed to lower levels of PBBs. Thus far, there is little convincing evidence linking exposure to PBBs and adverse health effects in Michigan farm residents. Although a variety of symptoms (neurological and neuropsychiatric, gastrointestinal, hepatic, dermal, musculoskeletal) have been reported, the prevalence of these symptoms has not been definitively linked to the extent or types of exposure. Also, neurodevelopmental effects in exposed children and immunological effects were reported. Physical examinations and laboratory tests have shown few abnormalities that corresponded to the complaints, and prevalence of symptoms has not been correlated with serum PBB levels. However, the possibility of long-term effects cannot be ruled out.

Most toxicity studies of PBBs in animals have involved oral exposure, and numerous effects have been documented including hepatic, renal, dermal/ocular, immunological, neurological, and developmental. Other effects of oral PBB exposure include decreased thyroid function, body weight loss, and liver cancer. Adverse hepatic as well as dermal and ocular effects have been observed in a limited number of dermal studies in animals. No significant adverse effects were observed in animal inhalation studies of PBBs, but only two studies have been conducted (one with octabromobiphenyl and one with decabromobiphenyl).

Thyroid Effects. The thyroid gland is an unequivocal target of PBBs in animals, and evidence in humans is suggestive of a similar relationship. Effects in workers exposed to unspecified PBBs and/or decabromobiphenyl included increased serum thyrotropin, low or borderline low serum thyroxine (T_4), and increased thyroid antimicrosomal antibody titers. A spectrum of effects has been observed in rats exposed for acute and intermediate durations, ranging from decreases in serum levels of serum T_4 and serum triiodothyronine (T_3) to histological and ultrastructural changes in the follicles. The preponderance of these studies tested FireMaster FF-1 or FireMaster BP-6 in rats, although chronic exposure to FireMaster FF-1 induced thyroid follicular hyperplasia in mice. Similar thyroid effects also occurred in offspring of treated rats and pigs.

Thyroid effects were produced in rats in acute-duration studies at doses as low as 3 mg/kg/day (reduced serum levels of T_4 hormone) but not at 1 mg/kg/day, in intermediate-duration studies at doses as low as 0.05 mg/kg/day (increased number and decreased size of follicles), and in chronic-duration studies at doses as low as 1.3 mg/kg/day. The no-observed-adverse-effect level (NOAEL) of 1 mg/kg/day is used herein as the basis for an acute-duration minimal risk level (MRL) for oral exposure. The acute-duration lowest-observed-adverse-effect level (LOAEL) for hepatic effects is identical to the LOAEL for acute thyroid toxicity, but is a less appropriate basis for the MRL because organ functional implications are not as clear. The intermediate-duration LOAELs for thyroid and hepatic effects are also comparable to each other, but neither of these LOAELs are suitable for an intermediate MRL because reproductive and developmental toxicity occurred at a lower dosage. The thyroid LOAEL for chronic-duration exposure is unsuitable for deriving a chronic MRL because decreased survival occurred at the same dose (lower doses were not tested), and thyroid, liver, and other effects occurred at lower doses in intermediate-duration studies.

Hepatic Effects. Histologically and ultrastructurally documented liver damage is a consistent and prominent finding among animals exposed to PBBs by the oral route, but studies of Michigan residents who were likely to have ingested PBB-contaminated food are inconclusive. The human studies do not demonstrate any clear association between abnormal liver-associated serum indices (serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], lactic dehydrogenase [LDH], bilirubin) or liver enlargement and PBB exposure. No information is available on hepatic effects of PBBs in humans exposed by the inhalation or dermal routes. Although the available studies on liver effects in humans are largely inconclusive, the animal data, as summarized below, suggest that humans may also be affected.

Hepatic effects ranging from microsomal enzyme induction and liver enlargement to fatty changes and necrosis have been observed in rodents and other laboratory animal species exposed orally to FireMaster PBBs in acute-, intermediate-, and/or chronic-duration studies. Acute- and intermediate-duration oral data for octabromobiphenyl mixtures are only available for rats and suggest that hepatic histopathologic effects are milder than for FireMaster mixtures at similar doses. Similarly, intermediate-duration oral data for decabromobiphenyl mixture suggest that this PBB mixture is a less potent hepatotoxicant than an octabromobiphenyl mixture. No pathologic effects were reported in the liver of rats exposed to an octabromobiphenyl mixture in acute- and intermediate-duration inhalation studies, or in an intermediate-duration study with a decabromobiphenyl mixture, but it is unclear if histology was evaluated following the intermediate-duration octabromobiphenyl mixture exposure. Acute dermal exposure to commercial

mixtures of hexabromobiphenyl, but not octabromobiphenyl, has been reported to produce gross necrotic changes in the liver of rabbits. Hepatocyte enlargement and degenerative changes (vacuoles or necrosis) are the most sensitive adverse hepatic effects that have been observed in the acute-, intermediate-, and chronic-duration oral studies with FireMaster PBBs. The lowest hepatic LOAELs for acute and intermediate durations are identical or essentially the same as the LOAELs for thyroid effects. The acute-duration LOAEL for thyroid toxicity is used as the basis for an acute oral MRL, but neither hepatic nor thyroid LOAELs for intermediate-duration exposure are suitable for MRL derivation because reproductive and developmental toxicity occurred at a lower dosage. Hepatotoxicity occurred at the lowest dosage tested in chronic studies with rats and mice, and the hepatic LOAEL in mice also caused thyroid effects. Neither the rat nor the mouse LOAEL is a suitable basis for a chronic MRL, however, due to decreased survival at the same dosage and weight loss and developmental toxicity in monkeys at a lower chronic dosage.

Altered vitamin A homeostasis, primarily manifested as decreased hepatic storage of vitamin A, is another established effect of PBBs in animals. Vitamin A is essential for normal growth and cell differentiation, particularly differentiation of epithelial cells, and some PBB-induced epithelial lesions resemble those produced by vitamin A deficiency. Because it is the primary storage site for vitamin A, the liver has a major role in retinol metabolism. Esterification of dietary vitamin A, hydrolysis of stored vitamin A, mobilization and release into the blood of vitamin A bound to retinol-binding protein, and much of the synthesis of retinol-binding protein occurs in the liver.

Immunological and Lymphoreticular Effects. Altered lymphocyte transformation responses among populations exposed to PBB following the Michigan contamination episode have been reported by some investigators. Others have not been able to confirm these findings. However, it is clear that no correlation can be established between altered immune parameters and PBB levels in serum. Some have suggested that PBBs associated with white blood cells is possibly the cause of the immunological dysfunction resulting from exposure to PBBs. This would imply that total PBB in plasma is not necessarily a good marker for immune dysfunction. Continuous examination of this cohort may resolve the controversy.

Studies in animals, mostly intermediate-duration studies in rodents, indicate that a variety of immunological parameters such as spleen and thymus weights, antibody production, and lymphoproliferative responses can be affected by treatment with commercial PBB mixtures. The only chronic study found increased splenic hematopoiesis in mice, but no histological changes in the spleen,

thymus, or lymph nodes of rats. It is apparent, however, that some of these effects are only seen at PBB levels that cause overt toxicity. Steroids are known to influence the immune response. Corticosterone levels were elevated in plasma of mice that were exposed to FireMaster BP-6 in the diet for 30 days, although the increase was not enough to be responsible for the observed immunological effect (reduced antibody-mediated response to sheep red blood cells). Thymic atrophy and a reduction in lymphocyte markers were reported in cows treated with PBB doses of 67 mg/kg/day for #60 days. However, these results should be interpreted with caution since the animals approached death at this dose. Based on the data available, it is difficult to suggest any particular species as the most sensitive. This is because different studies usually examined different end points, using different exposure protocols. It is unclear whether morphological changes in the reticuloendothelial system are more sensitive indicators of altered immune status than are functional changes. Although the limited data on humans are largely inconclusive, PBBs have altered immune responses in a variety of animal species, which suggests that humans may also be affected.

Neurological Effects. Data from studies on Michigan residents exposed to PBBs as a result of the 1973 feed contamination episode and data from a limited number of animal studies both suggest that exposure to PBBs may cause subtle effects on neuropsychological performance and development in humans. Symptoms of neurological effects, including fatigue, weakness, and decrements in the capacity to perform physical or intellectual work, were reported frequently by groups of farm families and residents of Michigan who were likely to have consumed farm products (milk, meat, and eggs) contaminated with PBBs; however, associations between PBB levels in serum or fat and the frequency of subjectively reported neurological symptoms were not found in several studies. The administration of neuropsychological tests to orally-exposed Michigan residents has not revealed abnormalities or associations between test performance and PBB levels in serum or fat. Similarly, no association between performance in neuropsychological tests and serum PBB levels was made in a study of a small number of chemical workers exposed to unspecified PBBs via inhalation and/or dermal contact.

Examinations of a small number of children (19) believed to have been exposed *in utero* or in early infancy during the peak of the Michigan PBB-feed contamination episode have not found consistent or marked effects on neuropsychological development. One study found a statistically significant association between performance in neuropsychological development tests and PBB levels in adipose tissues when the children were .2.5–4 years old, but a later examination when the children were .4–6 years old did not find such an association for the same tests.

Studies with rats have shown that oral exposure to PBBs at dose levels of . 10 mg/kg/day for intermediate durations (1–6 months) produced decreased motor activity and weakness of the hind limb , but not operant behavior deficits or histopathological alterations of brain or spinal nerve tissue. Performance deficits in tests of learning behavior were observed in the offspring of female rats and female mice treated with oral doses of PBBs at approximate daily dose levels ranging from 0.2 to 10 mg/kg during gestation and lactation. Effects on acquisition of forward locomotion, cliff avoidance, cage emergence, and open-field activity were found in offspring of rats that were exposed to 2 mg/kg/day from day 6 of gestation through day 24 postpartum and observed until postnatal day 60.

Dermal and Ocular Effects. Dermal lesions characterized as acne have been observed in humans occupationally exposed to PBBs. Increased prevalences of skin disorder symptoms, including rashes, acne, darkening or thickening of the skin, discoloration or deformity of fingernails or toenails, peeling and scaling, erythema, and hair loss, were reported by Michigan residents who were likely to have ingested PBB contaminated food. There was no association between serum PBB levels and prevalence of symptoms in one study, but physical examinations in the other study confirmed a slightly increased incidence of alopecia. Polymer fibers containing octabromobiphenyl mixture caused no dermal effects when placed on covered human skin for 6 days.

Acute-, intermediate-, and chronic-duration oral studies have found no histological alterations in the skin, pinnae, ear canals, or salivary glands of rats or mice exposed to FireMaster FF-1 or FireMaster BP-6. Alopecia, loss of eyelashes, generalized subcutaneous edema, dry scaly skin, and periorbital edema developed in three monkeys that were exposed to low doses of FireMaster FF-1 for several months; related histological findings included sebaceous gland atrophy and metaplasia and keratinization of hair follicles. Uncharacterized dermatosis was observed in similarly treated pigs. Hyperkeratosis of the eyelids and metaplasia of the tarsal glands with keratin cysts developed in cows that ingested FireMaster BP-6 for up to 60 days. Acute dermal application of FireMaster FF-1 induced hyperkeratosis, dilation and keratinization of hair follicles, and partial atrophy of the sebaceous glands in rabbits, but effects of octabromobiphenyl and decabromobiphenyl mixtures were generally mild (slight erythema and edema). Octabromobiphenyl mixture was not a sensitizer when applied to guinea pig skin. Although somewhat limited, the animal and human data are generally consistent and indicate that although PBBs can cause local responses such as irritation by direct dermal contact, exposure does not need to occur by the dermal route to produce cutaneous effects.

Unspecified signs of ocular irritation were observed in rats intermittently exposed to a high (5,000 mg/m^3) dust concentration of decabromobiphenyl mixture for 4 weeks, but severity was not reported, and recovery was not assessed. Octabromobiphenyl and decabromobiphenyl mixtures caused mild eye irritation in rabbits when applied as a dry solid. Histopathological changes have not been observed in the eyes of rats or mice exposed orally to FireMaster FF-1 or FireMaster BP-6 in studies of acute, intermediate, or chronic duration. Xerophthalmia (extreme dryness of the conjunctiva) was reported in rats fed FireMaster BP-6 in an intermediate-duration study. Based on effects in animals, direct exposure to PBBs is likely to be irritating to human eyes.

Body Weight Effects. Animal studies provide strong evidence that oral exposure to FireMaster PBBs causes a wasting syndrome characterized by progressive decreased weight gain, with immediate moderate to severe body weight loss generally preceding death. Effects on body weight have been observed in single dose, intermediate- and chronic-duration oral studies with rats, mice, guinea pigs, mink, monkeys, and/or cows. Changes in body weight were also observed in rabbits following acute dermal exposure to commercial mixtures hexabromobiphenyl, but not octabromobiphenyl, suggesting that the syndrome is independent of exposure route and is a potential effect of PBBs in humans.

Reproductive Effects. A limited amount of data are available regarding the reproductive effects of PBBs in humans. The distribution of sperm counts, sperm motility, and sperm morphology was investigated in a small number (50) of male Michigan residents who ingested food produced on PBB-contaminated farms or who worked in a PBB manufacturing company. The study found no evidence for PBB-related effects compared with a putatively unexposed control group. No relationship was found between serum PBB levels and frequency and duration of breast-feeding in a retrospective study of women exposed to PBBs during the Michigan episode. A study of fetal mortality rates in Michigan counties did not include data for fetal mortalities occurring during the first trimester of pregnancy.

Animal studies provide limited evidence that FireMaster FF-1 and FireMaster BP-6 PBBs cause adverse reproductive effects in a variety of species. Increased menstrual cycle duration and prolonged implantation bleeding were observed in female monkeys fed approximate daily dose levels of 0.012 mg/kg for 7 months before breeding and during pregnancy. A corresponding decrease in serum levels of progesterone suggests that the reproductive effects in the monkeys are related to PBB-induced endocrine imbalance. This dosage (0.012 mg/kg/day) is the lowest tested in any intermediate-duration study and also caused fetal deaths in the monkeys after . 1 year of exposure. Although the reproductive effects are less serious, concern for serious developmental toxicity following exposures of <1 year

precludes deriving an MRL for intermediate-duration exposure. Implantation was completely blocked in 40–67% of female rats treated with gavage dose levels $28.6 mg/kg on alternate days between gestation days 0 and 14 . Alterations in male reproductive organs were observed at doses that caused death in male rats (necrosis of the epithelial lining of the ductus deferens after 100 mg/kg for 4–5 weeks) and in a monkey (hypoactive seminiferous tubules after . 0.73 mg/kg/day for 25 weeks). No alterations in litter size or fertility were observed in a study of male and female minks fed #0.39 mg/kg/day for 6–7 months prior to breeding and during pregnancy or in the F_1 or F_2 generations of female parental rats fed as much as 5 mg/kg/day during the postimplantation phase of gestation and through weaning.

Based on the observations of adverse effects on reproduction in animals exposed to PBBs, the possibility that PBBs may cause reproductive harm in humans cannot be refuted and suggests that exposure of women to PBBs prior to and during the early phases of pregnancy may be of particular concern.

Developmental Effects. Consistent or marked abnormalities have not been found in examinations of the physical and neuropsychological development of children exposed *in utero* or in early infancy during the peak of the Michigan PBB episode. Likewise, a comparison of fetal mortality rates for Michigan counties with a high percentage of quarantined farms and those for Michigan counties with no quarantined farms did not clearly establish or refute the possibility that the Michigan PBB episode caused developmental problems in exposed people.

Fetotoxic and developmental effects have been observed in studies of FireMaster FF-1 or FireMaster BP-6 in several species of laboratory animals. Embryolethal effects or increased mortality among nursing young were observed in rats and mice after oral exposure during gestation and in monkeys after exposure before conception and during pregnancy. Because the dosage (0.012 mg/kg/day) causing these serious developmental effects in monkeys is the lowest tested in any chronic study of PBBs, it is not possible to derive an MRL for chronic-duration exposure. Structural malformations in fetuses, including cleft palate, were also observed in rats and mice after exposure to these PBBs during gestation. Increased incidences of fetuses with extra ribs were reported in a study of rats orally exposed to commercial octabromobiphenyl mixture during gestation, but oral exposure to commercial decabromobiphenyl mixture was not embryotoxic, fetotoxic, or teratogenic in rats. Studies with FireMaster FF-1 and FireMaster BP-6 found that body weight gain was reduced in the offspring of rats and mice after exposure during gestation, in rat offspring after exposure during gestation and lactation, and in mink kits after parental exposure before and during pregnancy. Liver effects, including increased liver weight and hepatic cytochrome P-450 enzymic activity, hepatocyte enlargement, vacuolization, and other

degenerative changes, were observed in the offspring of rats, mice, and/or swine fed FireMaster FF-1 or FireMaster BP-6 during gestation and/or lactation. Performance deficits in tests of operant behavior were observed in offspring of rats and mice after oral exposure to FireMaster FF-1 or FireMaster BP-6 during pregnancy and lactation.

Although the available human data regarding developmental effects of PBBs are inconclusive, the results from animal studies strongly suggest that PBBs may cause mild to severe developmental effects in humans, including growth retardation, alteration of neuropsychological development, and structural malformations.

Cancer. There is no epidemiological evidence of an association between exposure to PBBs and increased prevalence of cancer (all sites) in Michigan residents who were likely to have ingested PBB-contaminated food. These data are inconclusive due to a short latency period of 4 years. Suggestive relationships between increasing serum levels of PBBs and risks of breast cancer, digestive system cancer, and lymphoma (not otherwise specified) were found in case-control studies of Michigan PBB registry enrollees who were followed for approximately 20 years.

Oral studies with rats and mice demonstrate that FireMaster FF-1 is an unequivocal hepatocarcinogen. Hepatocellular adenomas, carcinomas, and/or liver neoplastic nodules were induced in these species following single or repeated (intermediate- and chronic-duration) exposures. These types of liver neoplasms even developed in the offspring of rats administered a single gavage dose during gestation or offspring of mice treated by diet during the perinatal period (throughout gestation and lactation). Liver neoplasm incidences were much higher in rats and mice exposed for up to 2 years in the only chronic bioassay than in the other studies that involved shorter-duration exposures of up to 6 months followed by an observation period of up to 2 years. Based on findings in male rats and mice of both sexes in this study, there is some evidence that combined perinatal and adult dietary exposure to FireMaster FF-1 enhanced the susceptibility of hepatocellular neoplasms in animals receiving adult exposure.

Tumors were not clearly or consistently observed in nonhepatic tissues of animals exposed to FireMaster FF-1. Induction of thyroid follicular cell adenoma was inconclusive in mice in both National Toxicology Program bioassays. Equivocal increases in incidences of mononuclear cell leukemia were observed in adult-only exposed rats in the NTP chronic study, and combined perinatal and adult exposure showed no significant increase. Combined analysis of the incidences of this leukemia in the adult-only, perinatal only, and combined perinatal and adult exposure groups, however, showed an apparent association

between increasing incidences and dose, and incidences in some of the groups exceeded historical control ranges. Evidence is available that oral administration of FireMaster BP-6 promotes development of initiated tumors in rats (liver enzyme-altered foci assays) and hamsters (tracheal papilloma assay).

Based on the results of the oral studies of FireMaster FF-1 in rats, there is sufficient evidence to conclude that PBBs are carcinogenic in animals and potentially carcinogenic in humans. PBBs as a group have been classified as possibly carcinogenic to humans by IARC (Group 2B). This classification is based on sufficient evidence for carcinogenicity to animals and inadequate evidence of carcinogenesis in humans. NTP concluded that PBBs are reasonably anticipated to be human carcinogens based on sufficient evidence of carcinogenicity in animals. The EPA has not classified the carcinogenicity of PBBs. Because there is insufficient information about which constituents of the PBB mixtures are carcinogenic and the congener profile to which people may be exposed environmentally is likely to be different from the original PBB source, it is assumed that PBB mixtures of any composition are potentially carcinogenic. This assumption has uncertainty since it cannot be verified with current knowledge, and because the mechanism of PBB carcinogenesis in rodents has not been definitively elucidated.

Polybrominated Diphenyl Ethers. Information is available on the health effects of all three commercial mixtures of PBDEs (deca-, octa-, and hexaBDEs), although the toxicology of these mixtures is less well characterized than for PBBs. Most of the data are from studies of orally exposed laboratory animals indicating that effects of decaBDE are generally much less pronounced than for octa- and hexaBDE mixtures following acute and repeated-dose exposures. This dissimilar toxicity is likely related to differences in absorption, metabolism, and elimination of the congeners in each mixture as shown by rodent toxicokinetic studies. In particular, in comparison with the other mixtures, decaBDE is minimally absorbed (0.3–2%), has a relatively short half-life (<24 hours), and is rapidly eliminated via fecal excretion (>99% in 72 hours). These toxicokinetic differences correlate with environmental monitoring data indicating that decaBDE has low bioaccumulation potential.

Available intermediate- and chronic-duration oral studies in animals indicate that the thyroid and liver are the main systemic targets of PBDE toxicity as shown by effects mainly including enlargement and histological alterations in both organs and changes in serum levels of thyroid hormones. Several acute-duration studies of pentaBDE suggest that immunosuppression may also be an important health end point. Very little information is available on potential neurotoxic effects of PBDEs, mainly the results of three behavioral tests showing alterations in the developing nervous system of mice following neonatal exposure to low doses of 2,2',4,4'-tetraBDE and 2,2',4,4',5-pentaBDE. Concern for neurodevelopmental

toxicity is raised by the PBDE-induced alterations in thyroid hormone homeostasis because development of the central nervous system is dependent on thyroid hormones. Information on the reproductive toxicity of PBDEs is limited to a one generation study of decaBDE in rats that found no exposure-related functional effects. Developmental toxicity studies have shown no evidence of teratogenicity of deca-, octa-, and pentaBDE in rats and rabbits, although fetotoxic effects, including skeletal ossification variations at maternally toxic doses, have occurred. Information on the carcinogenicity of PBDEs is limited to results of chronic oral bioassays on decaBDE that found limited evidence of cancer based on increased liver neoplasms in rats and mice and equivocal occurrence of thyroid tumors in mice. The weight of available genotoxicity evidence indicates that PBDEs are not genotoxic. Dermal application studies in rabbits showed that decaBDE, octaBDE, and pentaBDE were non-irritating to intact skin and caused some erythematous and edematous responses in abraded skin. DecaBDE was not a skin sensitizer in humans and octaBDE and pentaBDE were non-sensitizing in guinea pigs, indicating that the PBDEs did not cause delayed contact hypersensitivity.

Thyroid Effects. Limited information is available on thyroid effects in PBDE-exposed humans. There are suggestive occupational data as shown by effects that included increased serum FSH, low or borderline low serum T_4, and increased thyroid antimicrosomal antibody titers in workers exposed to decaBDE and/or unspecified PBBs. There was no clear association between plasma levels of 2,2',4,4-tetraBDE and thyroid hormone levels (free and total T_3 and T_4, TSH, free testosterone, follicle-stimulating hormone, lutenizing hormone, and prolactin) in men who consumed varying amounts of fatty fish from the Baltic Sea. Based on consistent evidence in animals, as summarized below, the thyroid is particularly sensitive to PBDEs and is a likely target of toxicity in exposed humans.

Thyroid effects that have mainly included reduced serum T_4 hormone levels and follicular cell hyperplasia were consistently observed in rats and mice orally exposed to PBDEs. Accompanying changes in serum TSH levels were not found and the depression of serum T_4 is likely related to hepatic enzyme induction. Acute duration studies showed decreases in serum T_4 in rats exposed to $10 mg/kg/day octaBDE or $30 mg/kg/day pentaBDE for 4 days and in rats and mice exposed to $18 mg/kg/day pentaBDE for 14 days. Effects observed in intermediate-duration studies include thyroid hyperplasia in rats exposed to $8 mg/kg/day octaBDE for 30 days and reduced serum T_4 in rats exposed to $10 mg/kg/day pentaBDE for 90 days. Exposure to pentaBDE on gestation day 6 through postnatal day 21 caused serum T_4 reductions at 30 mg/kg/day in maternal rats and $10 mg/kg/day in their fetuses and neonatal offspring. Intermediate-duration exposure to a 77% decaBDE/22% nonaBDE commercial mixture caused thyroid hyperplasia in rats at doses $80 mg/kg/day for 30 days. Chronic (103-week)

exposure to high-purity decaBDE ($97%) did not induce thyroid histopathological changes in rats at #2,550 mg/kg/day, although follicular cell hyperplasia developed in mice exposed to 2,240 mg/kg/day.

Hepatic Effects. The hepatotoxic potential of PBDE mixtures is well-documented in animals by oral exposure. The spectrum of observed hepatic effects includes microsomal enzyme induction, liver enlargement, and degenerative histopathologic alterations that progress to tumors. Repeated dietary exposure to PBDEs typically caused liver enlargement with or without degenerative changes, and effects were generally dose-related in incidence and severity, more frequent and pronounced in males than females, and more severe with octaBDE and pentaBDE than decaBDE. Hepatic effects induced by chronic exposure to decaBDE included degeneration and thrombosis in rats exposed to 2,240 mg/kg/day and centrilobular hypertrophy and granulomas in mice exposed to $3,200 mg/kg/day. Increased liver weight and hepatocellular enlargement with vacuolation occurred in rats exposed to pentaBDE doses as low as 2–9 mg/kg/day for 4–13 weeks. Increased incidences of degeneration and necrosis of individual hepatocytes were observed 24 weeks following exposure $2 mg/kg/day of pentaBDE for 90 days in rats. No studies are available on hepatic effects of PBDEs in humans. Based on the evidence in animals, PBDEs are potentially hepatotoxic in humans.

Immunological and Lymphoreticular Effects. Information regarding the immunosuppressive potential of PBDE mixtures is essentially limited to evidence from acute-duration oral studies of pentaBDE in animals. The plaque-forming splenic cell antibody response to injected sheep red blood cells was significantly reduced in mice exposed to 72 mg/kg/day pentaBDE for 14 days; single doses as high as 500 mg/kg had no effect. *In vitro* production of IgG immunoglobulin from pokeweed mitogen-stimulated splenocytes was reduced in mice exposed to 36 mg/kg/day pentaBDE for 14 days. Other 14-day studies in mice found no changes in natural killer cell activity to murine YAC-1 target cells at #72 mg/kg/day or numbers of splenic and thymic lymphocyte subsets at #36 mg/kg/day, although 18 mg/kg/day of the single congener 2,2',4,4'-tetraBDE caused significantly reduced numbers of total lymphocytes and CD4+, CD8+, and CD45R+ subtypes in spleen. Chronic ingestion of decaBDE caused splenic lesions (hematopoiesis, fibrosis, lymphoid hyperplasia) in rats exposed to $1,200 mg/kg/day for 103 weeks. No studies are available on immunological effects of PBDEs in humans. Due to the limited amount of data in animals, insufficient information is currently available to adequately characterize the human immunotoxic potential of PBDEs.

Developmental Effects. Oral developmental toxicity studies of deca-, octa-, and pentaBDE have shown no evidence of teratogenicity in animals. Gestational exposure to a high (1,000 mg/kg/day) but maternally nontoxic dose of decaBDE was fetotoxic in rats as shown by subcutaneous edema and delayed skull bone ossification. Commercial mixtures of octaBDE caused skeletal ossification variations in rats and rabbits at maternally toxic levels and other indications of fetotoxicity at lower doses. Effects of gestational exposure to octaBDE included minimally increased postimplantation loss in rats at $10 mg/kg/day, increased resorptions in rats at 25 mg/kg/day, and increased skeletal variations in rabbits at 15 mg/kg/day and rats at 50 mg/kg/day. No evidence of fetotoxicity was found in the only available study of pentaBDE in rats at maternally toxic doses #200 mg/kg/day. No studies are available on developmental effects of PBDEs in humans. Based on the evidence in animals, PBDEs are unlikely to cause developmental toxicity at expected levels of exposure.

Cancer. The only information regarding carcinogenicity of PBDEs in humans is available from a case-control study that found no clear association between risk of non-Hodgkin's lymphoma and exposure to 2,2'4,4'-tetraBDE in a small group of Swedish men and women.

Cancer data on PBDEs in animals are limited to results of studies on decaBDE mixtures. In a bioassay conducted by the NTP, male and female rats were exposed to decaBDE ($94% pure) in the diet in low doses of 1,120 and 1,200 mg/kg/day, respectively, and high doses of 2,240 and 2,550 mg/kg/day, respectively, for 103 weeks. Male and female mice were similarly exposed to low doses of 3,200 and 3,760 mg/kg/day, respectively, and high doses of 6,650 and 7,780 mg/kg/day, respectively. Incidences of neoplastic nodules in the liver were significantly increased in the male and female rats, and incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in the male mice. Slightly elevated incidences of thyroid gland follicular cell adenoma or carcinoma (combined) were additionally observed in exposed male mice, although the increases were not statistically significant. Carcinogenicity was additionally evaluated in rats that were exposed to 0.01, 0.1, or 1.0 mg/kg/day dietary doses of a 77.4% decaBDE mixture (containing 21.8% nonaBDPO and 0.8% octaDBDPO) for approximately 2 years. No exposure-related neoplastic changes were found, but the power of this study to detect carcinogenic effects is limited by the very low dose levels in comparison to those tested in the NTP bioassay.

Based on the limited evidence of carcinogenicity in animals in the NTP bioassay (significantly increased incidences of neoplastic liver nodules in rats and combined hepatocellular adenomas and carcinomas in mice), as well as the lack of human data, decaBDE has been classified in EPA Group C (possible human

carcinogen) and IARC Group 3 (not classifiable as to its carcinogenicity to humans). EPA Group D classifications (not classifiable as to human carcinogenicity) were assigned to nona-, octa-, hexa-, penta-, tetra-, tri-, and *p,p'*-diBDE based on no human data and no or inadequate animal data. The U.S. Department of Health and Human Services has not classified the carcinogenicity of any PBDE mixture.

2.3 MINIMAL RISK LEVELS (MRLs)

As indicated in Section 2.1, there are three-dimensional structural differences in PBBs and PBDEs that can influence the relative behavior of the chemicals in biological systems. Consequently, although there are some similarities in the health effects of PBBs and PBDEs, it cannot be assumed that corresponding PBDE and PBB congeners necessarily have the same toxicological and toxicokinetic characteristics. PBBs and PBDEs also share some toxicological properties with other structurally similar polyhalogenated aromatic compounds, particularly polychlorinated biphenyls (PCBs), chlorinated dibenzo-*p*-dioxins (CDDs), and chlorinated dibenzofurans (CDFs) (Agency for Toxic Substances and Disease Registry 1994, 1998, 2000). The toxicity of PCBs and PBBs is commonly classified as either "dioxin-like" or "non-dioxin-like" based on evidence that dioxin-like congeners act through the same Ah-receptor initial mechanism involved in 2,3,7,8-TCDD toxicity. The mechanism(s) of toxicity for non-dioxin-like PCB and PBB congeners is less clearly elucidated, but also may involve receptors (e.g., the estrogen receptor, the ryanodine receptor, and others). For PBDEs, the introduction of the ether bridge precludes clearly classifying the congeners as either "dioxin-like" or "non-dioxin-like". As discussed in Section 3.5, available studies of structure-induction properties, structure-affinity binding properties, and structure-toxicity properties suggest that some *ortho* substituted (non-dioxin-like) PBDE congeners can exhibit stronger affinity for the Ah receptor and exhibit stronger dioxin-type toxicity than their corresponding non-*ortho* substituted (dioxin-like) analogs (Chen et al. 2001; Howie et al. 1990). This is contrary to what is expected for the corresponding PCB and PBB congeners, and has been attributed to the greater distance between the two biphenyl rings in PBDE congeners, relative to PCBs and PBBs. In other words, introduction of *ortho* substitutions into PBDEs or PCDEs does not create a spatial impediment for the two phenyl rings to assume a semi-flat position with respect to each other as it does for PCBs or PBBs. This has implications not only for dioxin-type toxicities, but also for non-dioxin-type toxicities. For example, mono- and diortho-substituted PCBs exhibit neurotoxic properties, and structure-activity relationships have been established for various neurological end points (see Agency for Toxic Substances and Disease Registry 2000 for details). Although this has not been adequately examined for PBBs and PBDEs, it is reasonable to speculate that mono- and diortho-substituted PBDEs might not necessarily follow the potency rankings of mono- and diortho-substituted PCBs and PBBs.

The assumption that PBBs and PBDEs share many toxicological characteristics with PCBs also does not consider geometrical differences due to the higher atomic weight and considerably larger molecular volume of bromine compare to chlorine (Hardy 2000, 2002). These differences contribute to dissimilar physical/chemical properties that can influence the relative toxicokinetics and toxicities of the chemicals.

People are environmentally exposed to PBB and PBDE mixtures of different congeneric composition than the original commercial PBB and PBDE mixtures. Although the toxicity or potency of environmental PBB and PBDE mixtures consequently may be greater or less than that of commercial mixtures, there are insufficient mixture toxicity data on which to directly base MRLs for environmental PBBs and PBDEs. Due to the likelihoods that (1) multiple mechanisms (Ah-receptor-dependent mechanisms, Ah-receptor independent mechanisms, or both) may be involved in health effects induced by PBBs/PBDEs, (2) different PBB/PBDE congeners may produce effects by different mechanisms, and (3) humans are exposed to complex mixtures of interacting PBBs/PBDEs with differing biological activities, as well as to the lack of a suitable approach for quantitatively evaluating joint toxic action from concurrent exposures to PBBs, PBDEs, PCBs, CDDs, and/or CDFs in the environment, data from commercial PBB and PBDE mixtures are used to develop MRLs for assessing health risks from environmental exposures to PBBs or PBDEs.

Polybrominated Biphenyls

Inhalation MRLs

No MRLs have been derived for inhalation exposure to PBBs because human and animal data for all durations are either insufficient or lacking. Insufficiencies in the human inhalation data include mixed-chemical and unquantified exposures. The animal inhalation database is limited by inadequately reported studies and lack of any information on the mixtures likely to be most toxic (i.e., FireMaster PBBs).

Oral MRLs

- An MRL of 0.01 mg/kg/day has been derived for acute oral exposure (14 days or less) to PBBs.

The acute oral MRL was based on a NOAEL for decreased serum levels of thyroid T_4 hormone identified in groups of 8–11 male rats that were treated with 0, 1, 3, or 6 mg/kg/day doses of an unspecified mixture of PBBs in lecithin liposomes by gavage for 10 days (Allen-Rowlands et al. 1981). The MRL was

estimated by dividing the NOAEL by an uncertainty factor of 100 (component factors of 10 for animal to human extrapolation and 10 for human variability). Levels of serum T_4 were significantly ($p<0.05$) reduced at $3 mg/kg/day, indicating that the lowest dose (1 mg/kg/day) is the NOAEL. Decreased serum T_4 is considered adverse due to unequivocal evidence from numerous studies that the thyroid is a target of PBBs with a spectrum of effects, including decreases in serum T_3 and T_4 hormone, thyroid enlargement, effects in the follicular cells (e.g., reduced size, hyperplasia with columnar appearance and papillary projections), and accumulation of colloid droplets (Akoso et al. 1982b; Byrne et al. 1987; NTP 1983; Gupta and Moore 1979; Kasza et al. 1978a; Norris et al. 1975a, 1975; Sepkovic and Byrne 1984; Sleight et al. 1978). Additional information on the derivation of the acute-duration oral MRL for PBBs is provided in Appendix A.

Intermediate- and chronic-duration oral MRLs were not derived because serious developmental and reproductive effects were observed in monkeys that had been exposed to PBBs for durations that spanned the intermediate and chronic categories at the lowest dose tested in the database. This dose (0.012 mg/kg/day) caused increased menstrual cycle duration and implantation bleeding after 6–7 months of exposure and fetal deaths (fetal abortion and stillbirth) after ≥1 year of exposure in monkeys, with surviving infants having decreased birth weight and decreased postnatal weight gain (Allen et al. 1978, 1979; Lambrecht et al. 1978). Additionally, weight loss occurred in the maternal monkeys. The 0.012 mg/kg/day serious LOAEL for developmental and reproductive effects is lower than the lowest less serious LOAELs for thyroid effects in rats (0.05 mg/kg/day) (Akoso et al. 1982b) and hepatic effects in guinea pigs (0.04 mg/kg/day) (Sleight and Sanger 1976). Concern for serious developmental and reproductive toxicity following exposures of <1 year therefore precludes deriving an MRL for intermediate-duration exposure. Derivation of an MRL for chronic oral exposure is precluded by the serious developmental effect (stillbirth) that occurred following exposures exceeding 1 year in duration. The serious LOAEL in monkeys is lower than the lowest chronic dosages tested in other species (0.5 and 1.3 mg/kg/day in rats and mice, respectively) that caused decreased survival (NTP 1992). ATSDR's classification of LOAELs into less serious and serious effects is discussed in the introduction to Section 3.2.

Polybrominated Diphenyl Ethers

Available information on the toxicity of PBDEs indicates that the health effects of commercial decaBDE is generally much less pronounced than for the octa- and hexaBDE mixtures following acute and repeated-dose exposures. This dissimilar toxicity is likely related to the comparatively poor uptake and

rapid elimination of decaBDE, and is consistent with environmental monitoring data indicating that decaBDE has a low potential to degrade and bioaccumulate relative to the other mixtures. In contrast to commercial decaBDE, which typically contains $97% of the single congener, octaBDE and pentaBDE are comprised of multiple congeners that appear to more readily yield the lower-brominated tetraBDEs and pentaBDEs that predominate in the environment. Consequently, due to the lower toxicity and lower potential for environmental degradation and bioaccumulation of decaBDE in comparison to the octaBDE and pentaBDE mixtures, MRLs for PBDEs are based on health effects data for the lower-brominated mixtures.

Inhalation MRLs

No MRLs have been derived for inhalation exposure to PBDEs because available human and animal data for all durations are either insufficient or lacking.

Oral MRLs

- An MRL of 0.03 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to PBDEs.

The acute oral MRL is based on a NOAEL of 1 mg/kg/day for reduced serum levels of thyroid T_4 hormone in fetal rats that were exposed to octaBDE on days 4–20 of gestation (Zhou et al. 2002). The MRL was estimated by dividing the NOAEL by an uncertainty factor of 30 (component factors of 10 for animal to human extrapolation and 3 for human variability). A component factor of 10 was not used for human variability because the MRL is based on effects observed in a sensitive subgroup. Thyroid hormone levels were determined in Long-Evans rats that were administered a technical pentaBDE mixture (DE-71) in corn oil by gavage from gestation day (Gd) 6 through postnatal day (Pnd) 21, except for Pnd 0 (day of birth) (Zhou et al. 2002). Dams were sacrificed on Gd 20 and Pnd 22 and offspring were sacrificed on Gd 20 and Pnd 4, 14, 36, and 90). Study end points included serum total T_4 and T_3 concentrations measured at each age point. The maternal exposure to pentaBDE caused reductions in serum total T_4 that were significantly ($p<0.05$) different from controls in dams at 30 mg/kg/day on Gd 20 and Pnd 22 (48 and 44%, respectively, relative to controls), and in fetuses and offspring at $10 mg/kg/day on Gd 20 (at least 15% reduced) and Pnds 4 and 14 (50 and 64% maximal in the 10 and 30 mg/kg/day groups, respectively). The effect on T_4 concentrations in the offspring was age-dependent as values returned to control levels by Pnd 36. There were no exposure-related effects on serum total T_3 concentrations in the dams or offspring at any time, although T_3 was not be measured in fetuses on Gd 20

due to insufficient serum sample volume. The critical NOAEL of 1 mg/kg/day and LOAEL of 10 mg/kg/day for reduced serum T_4 hormone levels in fetal rats that were exposed to pentaBDE (Zhou et al. 2002) are supported by a NOAEL of 3 mg/kg/day and a LOAEL of 10 mg/kg/day for reduced serum T_4 levels in weanling (28-day-old) rats that were exposed to octaBDE for 4 days (Zhou et al. 2001). Data from other acute-duration studies of PBDEs that support the selection of the critical NOAEL and LOAEL include a NOAEL of 2.5 mg/kg/day and LOAEL of 10 mg/kg/day for fetotoxicity in rats exposed to octaBDE for 10 days during gestation (Life Science Research Israel Ltd. 1987), a NOAEL of 5 mg/kg/day and LOAEL of 15 mg/kg/day for fetotoxicity in rabbits exposed to octaBDE for 13 days during gestation (Breslin et al. 1989), and LOAELs of 18 mg/kg/day for reduced serum T_4 in rats and mice exposed to pentaBDE for 14 days (Fowles et al. 1994; Hallgren et al. 2001). Additional information on the derivation of the acute-duration oral MRL for PBDEs is provided in Appendix A.

- An MRL of 0.007 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to PBDEs.

The intermediate oral MRL is based on a LOAEL of 2 mg/kg/day for minimal liver effects in rats that were exposed to pentaBDE for 90 days (WIL Research Laboratories 1984). The MRL was estimated by dividing the LOAEL by an uncertainty factor of 300 (component factors of 3 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability). Groups of 30 male and 30 female Sprague-Dawley rats were exposed to pentaBDE (commercial mixture DE-71) in the diet at dosage levels of 0, 2, 10, or 100 mg/kg/day for up to 90 days. Study end points included clinical signs, body weight, food consumption, hematology, clinical chemistry (including serum T_3 and T_4), urine indices, gross pathology, and selected organ weights (brain, gonads, heart, liver, kidneys, thymus, and thyroid). Histological examinations were performed on liver, thyroid, thymus, kidney, and lung in all dose groups and in all tissues (comprehensive evaluation) at 0 and 100 mg/kg/day. Hepatocytomegaly was observed in males at 2 mg/kg/day and both sexes at $10 mg/kg/day. The hepatocytomegaly was similar in incidence and severity after 4 and 13 weeks of exposure, was dose-related with respect to severity (some affected hepatocytes had vacuoles that likely contained lipid), and was still observed in males at $10 mg/kg/day and females at 2 and 100 mg/kg/day at 24 weeks postexposure (in lessened severity and incidence). Examinations at 24 weeks following exposure also showed an increase in individual hepatocytes with degeneration and necrosis, effects that were considered to be likely exposure-related and indicative of final loss of previously damaged cells. No NOAEL was identified because liver changes were observed at all dose levels. Nonhepatic effects included increases in serum T_4 levels at $10 mg/kg/day and thyroid follicular cell hyperplasia at 100 mg/kg/day. Based on the observations of hypertrophy, mild degeneration, and slight necrosis, 2 mg/kg/day is considered to be a minimal LOAEL

for liver effects. Data from other intermediate-duration studies that support selection of the 2 mg/kg/day minimal LOAEL include hepatic LOAELs of 5 mg/kg/day for cytomegaly (with vacuolation and necrosis at higher doses) in rats exposed to octaBDE for 13 weeks (IRDC 1977), 8 mg/kg/day for hepatocellular enlargement and vacuolation in rats exposed to octaBDE for 30 days (Norris et al. 1973, 1975a), and 9 mg/kg/day for hepatocellular enlargement and increased liver weight in rats exposed to octaBDE or pentaBDE for 28 days (IRDC 1976). Other relevant effect levels from intermediate-duration studies include thyroid LOAELs of 8 mg/kg/day for hyperplasia in rats exposed to octaBDE for 30 days (Norris et al. 1973, 1975a), and 10 mg/kg/day for reduced serum T_4 levels in fetuses and neonatal offspring of rats that were exposed to pentaBDE from gestation day 6 through postnatal day 21 (Zhou et al. 2002). Additional information on the derivation of the intermediate-duration oral MRL for PBDEs is provided in Appendix A.

A chronic-duration oral MRL was not derived for PBDEs due to insufficient data. Two chronic studies of PBDEs were conducted. In one of the studies, Sprague-Dawley rats (25/sex/dose level) were fed a 77.4% pure decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for approximately 2 years (Kociba et al. 1975; Norris et al. 1975a). Evaluations that included clinical signs, body weight, food consumption, hematology, clinical chemistry, urine indices, and comprehensive histological examinations showed no exposure-related effects. In the other chronic study, decaBDE (94–97% pure) was fed to F344 rats (50/sex/dose level) in doses of 1,120/1,200 mg/kg/day (males/females) or 2,240/2,550 mg/kg/day, and B6C3F1 mice (50/sex/dose level) in doses of 3,200/3,760 mg/kg/day or 6,650/7,780 mg/kg/day, for 103 weeks (NTP 1986). Histopathological changes occurred in both species and included liver effects (degeneration and thrombosis) in male rats at 2,240 mg/kg/day, and liver (centrilobular hypertrophy and granulomas) and thyroid effects (follicular cell hyperplasia) in male mice at 3,200 mg/kg/day. The highest chronic NOAELs that can be identified in these studies are 1 mg/kg/day for the decaBDE/nonaBDE mixture (Kociba et al. 1975; Norris et al. 1975a) and 1,120 mg/kg/day for decaBDE (NTP 1986). Neither of these NOAELs is appropriate for estimation of a chronic MRL for all PBDEs due to insufficient sensitivity of the studies. In particular, using the NOAELs of 1 and 1,120 mg/kg/day and an uncertainty factor of 100, chronic oral MRLs derived from these studies would be 1.4 and 1,600 times higher, respectively, than the 0.007 mg/kg/day intermediate MRL. The relative insensitivity of the chronic studies appears to be related to low potency of decaBDE compared to the pentaBDE mixture tested in the critical intermediate-duration study. The low toxicity of decaBDE relative to lower-brominated mixtures is illustrated by comparison of liver effect levels in 13-week rat studies: LOAELs of 2 and 5 mg/kg/day were identified for pentaBDE and octaBDE, respectively, whereas 8,000 mg/kg/day (highest tested dose) is a NOAEL for decaBDE (IRDC 1977; NTP 1986; WIL Research Laboratories

1984). A similar pattern was observed for thyroid effects in the study used to derive the acute-duration oral MRL (Zhou et al. 2001) as summarized above. Due to the insufficiencies of the chronic data for MRL derivation, the intermediate oral MRL could also be used as a value for chronic exposure.